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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,810	02/04/2002	Eva-Marie Mandelkow	28384/38187	6127

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EXAMINER	
CHERNYSHEV, OLGA N	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 03/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,810	MANDELKOW ET AL.	
	Examiner	Art Unit	
	Olga N. Chernyshev	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-66* is/are pending in the application.

4a) Of the above claim(s) *41-66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 June 2002* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/244,603.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/11/2*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Sequence compliance

1. This application remains non-compliant with the requirements of 37 C.F.R. § 1.821 through 1.825 for reasons of record specifically articulated in the office communication mailed on December 29, 2003. Specifically, no sequence listing has been provided which includes the amino acid sequence presented on page 29 of the instant specification. Also, amino acid sequence presented at page 59 is not properly identified. In case these sequences are new, Applicant needs to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. §§ 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Election/Restrictions

2. Applicant's election with traverse of Group XXVII in Paper filed on October 01, 2003 is acknowledged. The traversal is on the ground(s) that antibodies recited in the instant claims "share a common utility and thus satisfy the unity of invention requirement" and, further, that

"each of the antibodies in the Markush group could easily be searched together with terms as simple as "phosphorylated tau" (section II of the Response). This is not found persuasive for the following reasons. The Examiner maintains that claims 33 and 34 are each improper Markush claims because the plurality of antibodies which bind to a specific tau epitope amino acid recited in these claims lack a common utility which is based upon a shared structural feature lacking from the prior art, emphasis added. Each of these antibodies are independent and distinct chemical compounds lacking either a common structural property which distinguishes them as a group from structurally related compounds of the prior art or which provides them with a common utility which is lacking from those prior art antibodies. The antibodies of the instant invention, as claimed, appear to distinguish specific distinct phosphorylated epitopes within tau protein. It is obvious that in this case the individual search for each single phosphorylated epitope ought to be performed to establish the novelty of the instant invention. Applicant is advised that claim 33, as written, encompasses a plurality of non-related antibodies that bind non-overlapping phosphorylated tau epitopes within tau protein sequences of SEQ ID NO: 1. As such, search for each of these antibodies would clearly be an undue burden on the Examiner.

The requirement is still deemed proper and is therefore made FINAL.

Claims 41-66 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper filed on October 01, 2003.

Claims 33-40, in so far as they encompass an antibody that binds phosphorylated tau epitope comprising phosphorylated residue 262 in SEQ ID NO: 1, are under examination in the instant office action.

Oath/Declaration

3. It appears that oath filed on February 04, 2002 does not comply with 37 CFR § 1.63, section (d, 1, iv), which states that "A copy of the executed oath or declaration filed in the prior application, showing the signature or an indication thereon that it was signed, is submitted for the continuation or divisional application." In the instant case, a copy of the oath filed in application 08/477, 648, as prior application, is presented, while the instant application appears to be a divisional of US application 09/640,737, as indicated in transmittal form and, accordingly, PALM records. Clarification and, if necessary, submission of a new oath is required.

Drawings

4. The figures of the instant application are presented on separate pages or in separate panels. 37 C.F.R. § 1.84(u) (1) states that when partial views of a drawing which are intended to form one complete view, whether contained on one or several sheets, must be identified by the same number followed by a capital letter. For example, the two pages of Figure 1 in the instant specification should be renumbered "Figure 1A" – "Figure 1B" rather than "Figure 1a, 1b". Applicant is reminded that once the drawings are changed to meet the separate numbering requirement of 37 C.F.R. § 1.84(u) (1), the specification should be amended to change the Brief Description of the Drawings and the rest of the specification to refer to each Figure accordingly.

If, for example, Figure 1 is divided into Figures 1A-1B, then the Brief Description and all the references to this figure in the specification must refer to this Figure in the same manner.

Furthermore, it appears that in some case discrepancies in description of the figures exist. For example, Figure 1b is described as containing parts (a) and (b) (see page 23 of the instant specification). However, parts (a) and (b) are not properly identified within Figure 1b.

Applicant is advised to review all the figures of the instant specification for proper presentation and identification.

Specification

5. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided (emphasis added). The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 33-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention.

Claims 33-40 are directed to an antibody that binds phosphorylated tau, wherein the antibody binds a tau epitope comprising a serine residue 262 in SEQ ID NO: 1 only when the serine residue is phosphorylated and to the methods of detecting a phosphorylated tau protein in a sample by using such antibody. However, the instant specification fails to provide enough guidance for one skilled in the art on how to make the claimed antibody, thereby requiring undue experimentation to discover how to use Applicant's invention, as currently claimed.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. *In re Wands*, 8 USPQ2d, 1400 (CAFC 1988).

The nature of the invention is the demonstration that phosphorylation of tau protein, Ser-Pro and Thr-Pro motifs and especially Ser 262, is specifically associated with Alzheimer's disease pathology (pages 79-82 of the specification). The art recognizes abnormal phosphorylation of tau protein as being associated with Alzheimer cytoskeletal pathology. Antibodies specifically binding different phosphorylated and dephosphorylated epitopes of human tau are also well described in the art (see, for example, references C12 and C15 of IDS of

the instant application filed on July 16, 2002, and also text on pages 4, 50-62 of the instant specification). Specifically, the following antibodies known in the prior art were used in binding assays described in the instant specification: AT8 (pages 50-53 and Figures 1-6), SMI31, SMI33, SMI34, SMI35, SMI310 and TAU1 (pages 58-62, Figures 12-14 and Table 1 on page 87, for example). It was concluded that the antibodies used in the experiments described in the instant disclosure bind different epitopes of tau in different stages of phosphorylation (pages 50-63) and, further, "[a]ll these antibodies known in the art have the disadvantage that none of them it is known whether they recognize an epitope which is uniquely characteristic for the Alzheimer's disease state" (middle at page 4).

The instant claims encompass an antibody that binds phosphorylated tau at Ser 262 position only when the serine is phosphorylated. While the skill level in the art is high, the level of predictability is low. The instant specification, as filed, fails to present any guidance on how to produce an antibody that binds to phosphorylated Serine at position 262 and does not bind native or dephosphorylated Serine at residue 262. There is no working examples or reliance on prior art presented in the instant disclosure sufficient to teach one skilled in the art how to make such antibody. A skilled artisan readily recognizes that the instant antibody, as claimed, must specifically recognize residue 262 of tau protein only in phosphorylated state, which implies that such claimed antibody would not bind an epitope where residue 262 is not phosphorylated and residue 263, for example, is.

Applicant's invention is predicated on the finding that certain motifs and positions in the structure of tau protein are critical for abnormal phosphorylation and, therefore, might be specifically implicated in Alzheimer's disease. Applicant further extrapolates this result into a

method for detecting phosphorylated tau by using antibodies that specifically recognize only Alzheimer's disease pattern of tau hyperphosphorylation. Accordingly, it would appear that Applicant provides a single finding (the finding), and then present an invitation to experiment to develop antibodies with unique binding capacities, and then to assay if these antibodies would specifically recognize Alzheimer's tau.

A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of *Genentec, Inc, v. Novo Nordisk*, 42 USPQ 2d 100,(CAFC 1997), the court held that:

"[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one can not following the guidance presented therein and produce the claimed antibody without first making a substantial inventive contribution.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 33-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claims 33 and 39 are vague and indefinite in so far as they employ the term "tau" as a limitation, followed by a reference to a residue located within SEQ ID NO: 1 without disclosing a connection between "tau" and the amino acid sequence. Applicant is advised that providing a reference to a precise amino acid sequence identified by a proper SEQ ID NO: at the first appearance of the recitation "tau" would obviate this ground of rejection.

9. Claim 39-40 recites the limitation "phosphorylated residue-binding antibody" in claim 33. There is insufficient antecedent basis for this limitation in the claim.

10. Claims 34-38 are indefinite for being dependent from indefinite claim.

Double Patenting

11. In view of the elected invention of an antibody that binds tau phosphorylated at residue 262 of SEQ ID NO: 1, Applicant is advised that should claim 33 be found allowable, claims 34-35 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. Also, should claim 39 be found allowable, claim 40 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

12. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Olga N. Chernyshev whose telephone number is (571) 272-0870. The examiner can normally be reached on Monday to Friday 9 AM to 5 PM ET.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on (571) 272-0871. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)0. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternative number. Faxed draft or informal communications with the examiner should be directed to (571) 273-0870. Official papers should NOT be faxed to (571) 273-0870.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Olga N. Chernyshev, Ph.D.

OLGA N. CHERNYSHEV, PH.D.
PATENT EXAMINER